Appendix A is a marked-up copy of the amended claims and Appendix B is a clean copy of the amended claims.

REMARKS

Claims 1-12 and 14-15 are presently pending in the captioned application. Claims 1-4, 6-8, 10-12, and 14-15 have been amended and claim 13 deleted without disclaimer or prejudice as to the subject matter expressed therein. No new matter within the meaning of 35 U.S.C. §132 has been added.

In response to the objection under 37 C.F.R. §§1.821-5 for sequence listings, Applicants proffer a computer readable copy and amended specification to be filed at a later date. Additionally, at that time, all remaining objections to the specification regarding margins, spelling and punctuation will be addressed.

The amendments are presented in the expectation that the amendments will place this application in condition for allowance. Accordingly, entry of the amendments is respectfully requested.

1. Rejection of claims 1-15 under 35 U.S.C. §112, second paragraph

The Office Action rejects claims 1-15 under 35 U.S.C. §112, second paragraph for the reasons outlined in the outstanding Office Action.

Applicants have amended claims 1-4, 6-8, 10-12, and 14-15 to particularly point and distinctly claim the subject matter of the invention thereby removing the basis for the rejection and objection of the claims. Applicants note that no reason was given for the rejection of claim 5 and thereby consider the rejection as improper. Regarding the rejection of claim 13, Applicants have deleted claim 13 without disclaimer or prejudice as to the subject matter contained therein.

Accordingly, Applicants respectfully submit that claims 1-12 and 14-15 as amended, particularly point out and distinctly claim the subject matter of the invention and request the Examiner to reconsider and withdraw the rejection under 35 U.S.C. §112, second paragraph.

2. Rejection of claims 1-15 under 35 U.S.C. § 103

The Office Action states that claims 1-15 are rejected under 35 U.S.C. § 103 as being obvious. The Office Action rejects claims 1, 2, and 5-14 over Nath et al. (Novel Met-Enkephalin Analogue, Pharm. Res. Vol. 31, No. 5, pages 269-273 (1995)) in view of Chiesi et al. (U.S. Patent No. 5,855,916); claims 1-3, 7-11, and 13 over European Patent Application No. 0 463 653 ("'653") in view of Nath et al.; claims 1, 2, 4, and 7-14 over Hora et al. (U.S. Patent No. 5,977,856) in view of Nath et al.; and claims 1, 7-13, and 15 over

French Patent 2 710 268 ("'268") in view of Nath et al.

Applicants respectfully traverse this rejection because all three prongs for a *prima facie* case of obviousness have not been established for each of the rejections. Specifically, all the claim limitations are not present in the cited references and one of ordinary skill in the art would have no motivation to modify the cited references into the present invention.

To establish a *prima facie* case of obviousness, the Examiner must establish: (1) that some suggestion or motivation to modify the references exists; (2) a reasonable expectation of success; and (3) that the prior art references teach or suggest all the claim limitations. Amgen, Inc. v. Chugai Pharm. Co., 18 USPQ2d 1016, 1023 (Fed. Cir. 1991); In re Fine, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); In re Wilson, 165 USPQ 494, 496 (C.C.P.A. 1970).

A *prima facie* case of obviousness must also include a showing of the reasons why it would be obvious to modify the references to produce the present invention. See Ex parte Clapp, 277 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). The Examiner bears the initial burden to provide some convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings. Id. at 974.

1. Rejection of claims 1, 2 and 5-14 over Nath et al. in view of Chiesi et al.

As a basis for the rejection the Office Action states:

> Claims 1, 2, and 5-14 are rejected under 103 U.S.C. 103(a) as being obvious over the Nath et al articles in view of Chiesi et al. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-ala-gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. . . .the Nath et al article does not teach the opioid peptide in combination with a cyclodextrin derivative,. Chiesi et al teach forming an inclusion complex of a basic drug and a Cyclodextrin derivative. Chiesi et al teach forming an inclusion complex of a basic drug and a cyclodextrin such as hydrooxypropyl-β-cyclodextrin and dimethyl-β-cyclodextrin. The inclusion complex results in improved storage stability and enhanced water solubility and Bioavailabilty for the drug. The drug is to be administered orally or parenterally. . . It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to combine the opioid peptide and cyclodextrin derivative in the above -outlined compositions because component proportion is an art-recognized result-effective variable which si routinely determined and optimized in the pharmaceutical arts.

In the present application, the cited references do not teach each and every limitation of the claimed invention. In particular, Nath et al. teaches a compound Tyr-D-Ala-Gly-MePhe-Gly-NHC_3H_7, which is not the peptide, L-Tyr-D-Ala-Gly-N-methylphenylalanyl-glycol-isopropylamide of the present invention.

The differences between the Nath et al. compound and the claimed compound include the lack of L and the lack of an

additional Ala in the Nath et al. compound. Moreover, the claimed compound is an amide whereas the Nath et al. compound is an amine. Accordingly, each and every limitation of independent claim 1 is not taught by Nath et al.

Applicants respectfully submit that the deficiencies of Nath et al. are not provided by Chiesi et al. Initially, Applicants note that Chiesi et al. fail to disclose the opioid peptides of the present inventive subject matter. Further, Chiesi et al. is limited to a multi-component inclusion complex consisting of a basic drug with the basic drug being an acid, wherein the important aspect lies in enhanced water solubility of the multi-drug complexes in the presence of an acid. See column 1, lines 53-63. However, the present invention is an amide, which does not require improved water solubility or stability.

Furthermore, the Office Action fails to show that one of ordinary skill in the art would be motivated to make the claimed combination. In particular, one of ordinary skill in the art would not be motivated to make the claimed invention based on a reference teaching water solubility where improved water solubility is not an object of the invention.

A *prima facie* case of obviousness is not satisfied because each and every claimed element is not present. Accordingly, Applicants respectfully submit that the presently claimed invention

is unobvious over Nath et al. in view of Chiesi et al. and respectfully request the Examiner to reconsider and withdraw the rejection of claims 1, 2 and 5-14.

2. Rejection of claims 1-3, 7-11, and 13 over EP '653 in view of Nath et al.

As a basis for the rejection the Office Action states:

> Claims 1-3, 7-11, and 13 are rejected under 103 U.S.C. 103(a) as being obvious over the European Patent Application '653 in view of the Nath et al article. The European Patent Application '653 teaches combining drugs, including peptide drugs such as enkephalin, with cyclodextrin, especially B-cyclodextrin. The combination permits the drugs to be administered nasally, thereby avoiding the problems of poor absorption after oral administration and avoiding undesirable metabolism of the drugs. . . . The European Patent application does not teach administration of Applicant's particular opioid peptide. The Nath et al. article teaches the highly active opioid peptide L-Tyr-D-ala-gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. . . . It would have been obvious to one of ordinary skill in the art to at the time Applicant's invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulation of the European Patent Application '653 and because administering the opioid peptide of Nath et al nasally in the pharmaceutical formulations of the European Patent Application '653 would avoid problems of poor absorption after oral administration and of undesirable metabolism as taught by the European Patent Application '653. It would further have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine

> all operable and optimal ratios of opioid pepitde and β-cyclodextrin in the above outlined compositions because and dimethyl-β-cyclodextrin. The inclusion is an art-recognized result-effective variable which si routinely determined and optimized in the pharmaceutical arts.

Again, the cited references do not teach each and every limitation of the claimed invention insofar as Nath et al. does not teach the L-Tyrosyl-D-Ala-Gly-N-methylphenylalanyl-glycol-isopropylamide of the present invention. As is discussed above, the differences between the Nath et al. compound and the claimed compound include the lack of L and the lack of an additional Ala. Moreover, the claimed compound is an amide whereas the Nath et al. compound is an amine. Accordingly, each and every limitation of independent claim 1 is not taught by Nath et al.

Applicants respectfully submit that the deficiencies of Nath et al. are not provided by EP '653. Initially, Applicants note that EP '653 fails to disclose the opioid peptides of the present inventive subject matter. Further, the '653 reference teaches combining drugs including peptide drugs such as enkephalin with cyclodextrins. The reference further teaches that undesirable side-effects due to using an absorption enhancer alone may be avoided when an absorption enhancer is used in combination with a cyclodextrin. See Column 3, lines 9-15. However, the presently claimed invention relates to inclusion complexes having a long

duration of activity and improved efficacy.

Moreover, one of ordinary skill in the art would not be motivated to make the claimed combination since the opioid of the present invention is already stable and capable of being absorbed. No addition of an absorption enhancer is required.

A *prima facie* case of obviousness is not satisfied because each and every claimed element is not present. Accordingly, Applicants respectfully submit that the presently claimed invention is unobvious over European Patent Application No. 0 463 653 in view of Nath et al. and respectfully request the Examiner to reconsider and withdraw the rejection of claims 1-3, 7-11, and 13.

3. Rejection of claims 1, 2, 4, and 7-14 are rejected over Hora et al. in view of Nath et al.

As a basis for the rejection the Office Action states:

> Claims 1, 2, 4 and 7-14 are rejected under 103 U.S.C. 103(a) as being obvious over Hora et al in view of the Nath et al article. Hora et al teach conbing polypeptide drugs with cyclodextrin, B-cyclodextrin,, including hydroxyethyl-B-cyclodextrin. The combination improves the solubility and the stability of polypeptide drugs, and permits oral administration as well. . . . Hora et al do not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-ala-gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. . . . It would have been obvious to one of ordinary skill in the art to at the

> time Applicant's invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulation of Hora et al because the opioid peptide of the Nath et al article is a specific known example of the polypeptide drugs which are contemplated by Hora et al and because administering the opioid peptide of Nath et al in the pharmaceutical formulations of Hora et al. would improve the solubility and the stability of the opioid peptide as taught by Hora et al. It would further have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal ratios of opioid pepitde and β-cyclodextrin in the above outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical arts.

Yet again, the cited references do not teach each and every limitation of the claimed invention insofar as Nath et al. does not teach the L-Tyrosyl-D-Ala-Gly-N-methylphenylalanyl-glycol-isopropylamide of the present invention. The differences between the Nath et al. compound and the claimed compound include the lack of L and the lack of an additional Ala. Moreover, the claimed compound is an amide whereas the Nath et al. compound is an amine.

Applicants respectfully submit that the deficiencies of Nath et al. are not provided by Hora et al. Initially, Applicants note that Hora et al. fails to disclose the opioid peptides of the present inventive subject matter. The presently claimed invention relates to inclusion complexes having a long duration of activity and improved efficacy whereas Hora et al. teaches a method of

stabilizing polypeptides using cyclodextrin. Clearly, the opioid peptide of the present invention is not taught by Hora et al.

Additionally, one of ordinary skill in the art would not be motivated to make the claimed combination. In particular, the opioid of the present invention is already stable and capable of being absorbed. One of ordinary skill in the art would not be motivated to make the claimed invention based on a method of stabilizing polypeptides using cyclodextrin.

A *prima facie* case of obviousness is not satisfied because each and every claimed element is not present. Accordingly, Applicants respectfully submit that the presently claimed invention is unobvious over Hora et al. in view of Nath et al. and respectfully request the Examiner to reconsider and withdraw the rejection of claims 1, 2, 4, and 7-14.

4. Rejection of claims 1, 7-13, and 15 are rejected over French Patent '268 in view of Nath et al.

As a basis for the rejection the Office Action states:

> Claims 1, 7-13, and 15 are rejected under 103 U.S.C. 103(a) as being obvious over the French Patent '268 in view of the Nath et al article. The French Patent '268 teaches combining drugs, including analgesics and peptide hormones, with B-cyclodextrin. The combination permits the drugs to be administered transcutaneously. See the attached abstract. The French patent '268 does not teach administration of Applicants' particular opioid peptide. The Nath et al

> article teaches the highly active opioid peptide L-Tyr-D-ala-gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. . . . It would have been obvious to one of ordinary skill in the art to at the time Applicant's invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulation of French Patent '268 because the opioid peptide of the Nath et al article is a specific known example of the analgesic drug which are contemplated by the French patent '268, because the French patent '268 would have been expected to be useful in transcutaneously administering polypeptides such as the opioid peptide of the Nath et al because of the French Patent's '268 disclosed ability to administer polypeptide hormones, and because administering formulations would improve the solubility and the stability of the opioid peptide as taught by Hora et al. It would further have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical arts.

Still yet again, the cited references do not teach each and every limitation of the claimed invention insofar as Nath et al. does not teach the L-Tyrosyl-D-Ala-Gly-N-methylphenylalanyl-glycol-isopropylamide of the present invention. The differences between the Nath et al. compound and the claimed compound include the lack of L and the lack of an additional Ala. Moreover, the claimed compound is an amide whereas the Nath et al. compound is an amine.

Applicants respectfully submit that the deficiencies of Nath et al. are not provided by French Patent '268. Initially, Applicants note that French Patent '268 fails to disclose the opioid peptides of the present inventive subject matter. The presently claimed invention relates to inclusion complexes having a long duration of activity and improved efficacy whereas French Patent '268 teaches absorption promoters in the preparation of pharmaceutical compositions for transcutaneous administration. Clearly, the claimed limitation are not taught by French Patent '268.

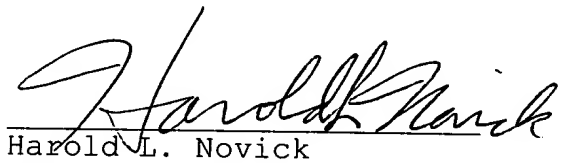
Additionally, one of ordinary skill in the art would not be motivated to make the claimed combination. In particular, the opioid of the present invention is already stable and capable of being absorbed. One of ordinary skill in the art would not be motivated to make the claimed invention based on a reference teaching absorption promoters in the preparation of pharmaceutical compositions for transcutaneous administration.

A *prima facie* case of obviousness is not satisfied because each and every claimed limitation is not present. Accordingly, Applicants respectfully submit that the presently claimed invention is unobvious over French Patent '268 in view of Nath et al. and respectfully request the Examiner to reconsider and withdraw the rejection of claims 1, 2, 4, and 7-14.

CONCLUSION

In light of the foregoing, Applicants submit that the application is now in condition for allowance. The Examiner is therefore respectfully requested to reconsider and withdraw the rejection of the pending claim and allow the pending claim. Favorable action with an early allowance of the claims pending is earnestly solicited.

Respectfully submitted,
NATH & ASSOCIATES PLLC



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BOX PATENT
Attorney Docket No. 82239

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Group Art Unit: 1653
	)	
DWIVEDI et al.	)	Examiner: J. RUSSEL
	)	
Serial No. 09/537,088	)	
	)	
Filed: March 29, 2000	)	

For: **NOVEL INCLUSION COMPLEXES OF A HIGH POTENT OPIOID PEPTIDE, PHARMACEUTICAL COMPOSITIONS AND METHOD OF TREATMENT**

Appendix A

Please amend the following claims as indicated in the following marked-up copy of the claims.

1. (Amended) An orally efficacious and prolonged duration of action inclusion complex, comprising [Inclusion complexes having significantly improved oral efficacy and prolonged duration of action selected from the group consisting of] an [highly potent] opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and [with] a cyclodextrin derivative.

2. (Amended) Inclusion complex as claimed in claim 1, wherein the cyclodextrin derivative is selected from beta cyclodextrin, hydroxypropyl-beta cyclodextrin, dimethyl-beta cyclodextrin, and hydroxyethyl-beta-cyclodextrin.

3. (Amended) Inclusion complex as claimed in claim 1 comprising

L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with beta[,]-cyclodextrin.

4. (Amended) Inclusion complex as claimed in claim 1 comprising L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with hydroxyethyl [hydroxyehtyl] beta-cyclodextrin.

6. (Amended) Inclusion complex as claimed in claim 1 comprising L-Tyrosyl-D-alanyl-glycyl [glycy]-N-methylphenylalanyl-glycyl-isopropylamide with dimethyl beta[,]-cyclodextrin.

7. (Amended) Inclusion complex as claimed in claim 1 wherein the molar ratio between L-Tyrosyl-D-alanyl-glycyl [glycy]-N-methylphenylalanyl-glycyl-isopropylamide and said cyclodextrin derivative is 1:5 to 2:1.

8. (Amended) Pharmaceutical compositions comprising a therapeutically effective amount of inclusion complex of L-Tyrosyl-D-alanyl- glycyl [glycy]-N-methylphenylalanyl-glycyl-isopropylamide with the [beta-] cyclodextrin derivative as claimed in claim 1 [claim1] having improved analgesic activity with longer duration of action as compared with the free peptide.

10. (Amended) Pharmaceutical composition as claimed in claim 8 formulated in a [various] physical [forms] form selected from the group consisting of [such as] tablets, injections, and capsules.

11. (Amended) A method for the treatment of acute inflammations and for alleviating pain comprising the step of administration of a pharmaceutical composition containing [containg] the inclusion complex as claimed in claim 1 to a patient in need thereof.

12. (Amended) A method as claimed in claim 11 wherein the inclusion complex is administered orally or transdermally or by a rectal route

13. (Deleted) [A method as claimed in claim 11 wherein the pharmaceutical composition of claim 8 exhibits significant analgesic activity with reduced dependence liability, respiratory depression, gastric irritation and sedation.]

14. (Amended) A method as claimed in claim 11 for the treatment of acute inflammations and for alleviating pain, which comprises an oral administration of inclusion complex of L-Tyrosyl-D-

alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with said [beta-] cyclodextrin derivative [as claimed in claim 1].

15. (Amended) A method for the treatment of acute inflammations and for alleviating pain, which comprises a topical application of inclusion complex of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with the [beta-] cyclodextrin derivative as claimed in claim 1.

BOX PATENT
Attorney Docket No. 82239

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Group Art Unit: 1653
	)	
DWIVEDI et al.	)	Examiner: J. RUSSEL
	)	
Serial No. 09/537,088	)	
	)	
Filed: March 29, 2000	)	

For: **NOVEL INCLUSION COMPLEXES OF A HIGH POTENT OPIOID PEPTIDE, PHARMACEUTICAL COMPOSITIONS AND METHOD OF TREATMENT**

Appendix B

Please amend the following claims as indicated in the following clean copy of the claims.

1. (Amended) An orally efficacious and prolonged duration of action inclusion complex, comprising an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a cyclodextrin derivative.

2. (Amended) Inclusion complex as claimed in claim 1, wherein the cyclodextrin derivative is selected from beta cyclodextrin, hydroxypropyl-beta cyclodextrin, dimethyl-beta cyclodextrin, and hydroxyethyl-beta-cyclodextrin.

3. (Amended) Inclusion complex as claimed in claim 1 comprising L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with beta-cyclodextrin.

A1

4. (Amended) Inclusion complex as claimed in claim 1 comprising L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with hydroxyethyl beta-cyclodextrin.

6. (Amended) Inclusion complex as claimed in claim 1 comprising L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with dimethyl beta-cyclodextrin.

A2

7. (Amended) Inclusion complex as claimed in claim 1 wherein the molar ratio between L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and said cyclodextrin derivative is 1:5 to 2:1.

8. (Amended) Pharmaceutical compositions comprising a therapeutically effective amount of inclusion complex of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with the cyclodextrin derivative as claimed in claim 1 having improved analgesic activity with longer duration of action as compared with the free peptide.

A3

10. (Amended) Pharmaceutical composition as claimed in claim 8 formulated in a physical form selected from the group consisting of tablets, injections, and capsules.

11. (Amended) A method for the treatment of acute inflammations and for alleviating pain comprising the step of administration of a pharmaceutical composition containing the inclusion complex as claimed in claim 1 to a patient in need thereof.

12. (Amended) A method as claimed in claim 11 wherein the inclusion complex is administered orally or transdermally or by a rectal route

A3

[13. (Deleted)]

14. (Amended) A method as claimed in claim 11 for the treatment of acute inflammations and for alleviating pain, which comprises an oral administration of inclusion complex of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with said cyclodextrin derivative.

15. (Amended) A method for the treatment of acute inflammations and for alleviating pain, which comprises a topical application of inclusion complex of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with the cyclodextrin derivative as claimed in claim 1.